PERMIT – PERsonalised MedicIne Trials

Review of methods used to assign treatment options to patient clusters

Deliverable 2.3

Lay Summary

1. Initial State of Play

Personalised medicine (PM) stems from the broad concept that managing a patient's health should be based on the individual patient's specific characteristics, including age, gender, height/weight, diet, environment, etc.

The concept of PM will impact how pharmacological treatments are discovered and developed, how patients are diagnosed and treated, and how health care systems allocate their resources to maximize patient benefits.

PM may be considered an extension of traditional approaches to understanding and treating disease. Ideally, it could serve to take clinical decisions based on a patient's profile (often molecular, but the concept is broader) to minimise harmful side effects, ensure a more successful outcome, and **possibly help contain costs** compared with a "trial-and-error" approach to disease treatment.

A broad community of stakeholders, including funders and people involved in medical research and care, are increasingly concerned with ensuring that **the right patient receives the right therapy, at the right dose and at the right time**.

Regardless of the application, any approach to PM should undergo different phases: discovery, validation and definition of usefulness from a clinical perspective.

Robust methodological approaches are needed to deal with the complexity and heterogeneity of the process, as well as the range of possible applications to stratification using multidimensional data (what is meant among other aspects, by "molecular profiling").

To make PM promises a reality, there is a need for more resources invested into validating biomarkers, identifying the suitable pre-clinical models, and demonstrating clinical efficiency today. The identification of bottlenecks and challenges of pre-clinical methods is one of the first step in defining **a shared PM development strategy** that can lay the foundation for more successful clinical trials across the sector.

Therefore, the scope of this work was to conduct a literature review and focus on the preclinical

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methodologies, highlighting advantages and disadvantages of the existing pre-clinical model systems used for PM approaches, as well as the emerging models proposed to replace the traditional animal models. In addition, the methods were assessed for 1. clinical relevance, 2. validity, 3. predictive value and 4. interpretation of the models in the context of PM (Ability of the model to discriminate between responders and non-responders for a given treatment). **Two case models were chosen: oncology as being the most advanced in the field of PM, and brain disorders, in particular, mental, neurodegenerative and neurodevelopmental diseases.**

Personalised medicine research

The PERMIT project mapped the general concept of methods for PM, to set the basis for the discussion on robustness and reproducibility of PM development programmes. The final goal is the identification of standards and the development of recommendations in terms of methodology of data generation, management, analysis, preclinical development and clinical trial design to improve clinical studies in PM.

The members of the PERMIT project group agreed on a common operational definition of PM research: **a set of comprehensive methods, (methodological, statistical, validation or technologies) to be applied in the different phases of the development of a personalised approach to treatment, diagnosis, prognosis, or risk prediction.** Ideally, robust and reproducible methods should cover all the steps between the generation of the hypothesis (e.g., a given stratum of patients could better respond to a treatment), its validation and pre-clinical development, and up to the definition of its value in a clinical setting.

2. Identifying the problem

Before initiating the literature review (a scoping review study), the main research questions were defined.

The main research questions addressed for oncology were:

- *Which pre-clinical models are currently used to provide validity data (i.e. the model can successfully discriminate between successful and unsuccessful treatments for the human disease condition) prior to therapeutic clinical trials of PM in oncology?*
- *What are the pros and cons of the various pre-clinical methods in oncology?*
- *Are the current pre-clinical models predictive for PM trial outcome in oncology?*

The main research questions addressed for brain disorders were:

- *Which pre-clinical models are currently used to provide validity data prior to*

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therapeutic clinical trials of PM in brain disorders?

- *What are the pros and cons of the various pre-clinical methods in brain disorders?*
- *Are the current preclinical models predictive for the outcome of PM trials?*

3. Main Outcomes

In oncology, a total of 63 studies met the inclusion criteria of the study. These were reviewed for quantitative and qualitative analysis, and the outcomes when it comes to the pathophysiology of the disease. Important aspects considered were the importance of inter- and intra-tumour heterogeneity; the critical role of the tumour microenvironment; and the involvement of the immune system. The literature review highlighted that there is a **lack of fully developed and reliable preclinical technologies that can navigate the complex variables in therapeutic responses and diagnostic accuracy in the cancer field**.

In brain disorders, a total of 94 studies met the inclusion criteria and were included in the analysis. **Despite the large use and development of pre-clinical models in brain disorders, their application for PM approaches is not a reality yet**. In fact, to date there are fundamental gaps that prevent their broad implementation in personalised central nervous system illness management.

Our results highlighted more fundamental issues in preclinical research. First, despite technical advances and more sophisticated preclinical models, to date there are **knowledge gaps in biology and an inability to fully recapitulate human diseases in models**.

Lack of methods reporting is a major problem. The access to the preclinical data supporting clinical trials is challenging, there is a lack of systematic reviews and methods are often not reported in sufficient detail. Another problem is the failure to systematically validate the model systems, both in terms of internal validity (the experiments ability to identify causal relationships) and external validity. All together, these gaps are threatening the quality and reliability of preclinical studies results.

In addition, as with many emerging technologies, the enthusiasm surrounding PM is tempered by uncertainties in regulatory aspects. As the shift to PM is younger than the laws that otherwise regulate the medical and research fields, there are gaps between technology and oversight in the preclinical phase.

A relevant point to be addressed is also the **low availability of negative data**. Negative results are not appealing for publication, meaning that the results of thousands of experiments that

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fail to confirm the reliability of pre-clinical models do not see the light of day.

4. Gaps identified

In order to allow for the implementation of PM, there has to be availability of appropriate preclinical models which can be relied upon to generate accurate and predictive data. The main gaps identified in the field are:

The first gap relates to the fact that there is a **lack of clinically relevant experimental models for PM**. The reason for this is partly that there are no direct requirements to demonstrate the relevance of models, but it is also explained by the fact modelling PM is extremely complex, and there is a need for further technological advances in this area.

The second gap we identified was the **lack of standards for methods, validation procedures and the lack of quality assessment systems**. The fact is that preclinical models are often not robust enough for translation. Hurdles for model validation are that this type of work is not academically rewarded, it is time consuming and expensive.

The third gap is the **lack of accurate reporting and the lack of reporting negative results**, which then further leads to a lack of systematic reviews and meta-analyses on methods, and these are important tools for evidence-based medicine. Reporting guidelines exist, but there is often no compliance with the recommendations, and again the academic reward system for publishing positive results, as well as the competitive secrecy from industry, means that negative findings are often not shared.

The fourth gap relates to regulation, and the **lack of harmonised guidelines for evaluating the relevance and robustness of preclinical evidence**.

The last gap we identified is the **lack of involvement between preclinical and clinical research**, and the need for a better definition for patient engagement.

5. Building on these results

The next step in the PERMIT project was to integrate the findings here reported with the results of a survey carried out with representatives from the pharmaceutical industry, aiming to map preclinical strategies currently undertaken by industry. The results of the survey enabled a better understanding of the challenges and opportunities in the translational development phase of PM clinical trials. Furthermore, departing from this gap analysis, and the consensus reached during a series of consultation meetings, we have constructed a set of 15 recommendations for robust and reproducible research in personalised medicine. The recommendations are focused around five main areas: 1) clinically relevant translational research; 2) robust model development; 3) transparency and education; 4) revised regulation; and 5) interaction with clinical research and patient engagement

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